Description

Medical device for dispensing medicaments

This invention relates to a medical device that dispenses drugs for the selective treatment of specific tissues or organ parts and to a method of manufacturing such drug-coated devices.

Numerous diseases do not affect the entire organism at the same time but are restricted to specific types of tissue, often even to individual tissue areas or organ parts. Examples can be found among tumor, joint and vascular diseases.

Pharmaceutical treatment of such diseases generally consists in oral or intravenous administration of drugs that spread throughout the body and cause undesirable side effects in healthy tissues and organs, especially when the disease to be treated is severe. This is a treatment constraint. The diseased tissues could be treated either selectively using drugs that specifically bond to diseased tissue (such as antibodies) while the administration path is maintained, or by selective administration such as direct injection into the diseased tissue or supply via a catheter to the blood vessels that feed the diseased tissue. Selective administration may cause problems due to the short efficacy period of the drugs and the invasive administration paths, as repeated administration is not an option. When drugs are administered via the bloodstream that feeds the diseased tissue, there is the additional problem that the drugs are insufficiently extracted when the blood or active agent solution swiftly flows through the blood vessels.

These problems used to be addressed by various pharmaceutical preparations with delayed release of the active agent, drug-dispensing implants or selective access paths that stay operational for a longer period of time such as implanted catheters, etc.

It is known that the surface of medical equipment inserted into the body, in particular, of catheters, can be coated with agents that enhance gliding quality or prevent blood coagulation but have no therapeutic effect.

In addition, catheters are equipped with special devices for injecting drugs into the arterial wall, for example, using needles or a perforated catheter wall that sits close to the tissue wall and through which the drug is injected at high pressure.

Other principles are based on extending the contact time between the arterial wall and an active agent preparation administered via the catheter by either blocking the blood flow for a sufficient period of time, e. g. using dual balloon catheters in which the active agent solution is contained in a chamber between the balloons, or by voids between a toric outer wall of the balloon allowing a limited flow of blood through a canal that passes through the balloon.

According to US 5 102 402, drugs in the form of microcapsules are inserted into preformed recesses of balloon catheters for delayed release of the active agent. When the balloon is inflated, the microcapsules are to be pressed against the vessel wall, remain there and slowly release the active agent(s). Many authors propose to apply drugs embedded in hydrogel onto balloon catheters while they do not specify the function of the hydrogel, i. e. to act as an adhesive, to improve the gliding quality, or for controlled drug release.

A disadvantage of the products mentioned above is their complex structure which causes production, quality control, and cost problems and forces additional aggravating working steps on doctors and patients when applied. Some of the methods mentioned may result in undesirable vascular damage in excess of the intended dilatation of the vessel. Another setback is that each measure aimed at extending contact time entails another reduction with blood and oxygen supply to the downstream tissues.

For the sake of completeness, we also refer to an apparatus for preventing restenosis as described in WO 01/24866 that is coated with a lipid ceramide substance derived from natural cell membranes. This substance is used because of its affinity to cell walls that is not found in common drugs. Expert authors continue to state that restenosis prevention using drugs requires release of the active agent over a period of several days.

It is the problem of the invention to provide an apparatus for the controlled release of drugs into specific tissue areas or organ parts that has a strong therapeutic effect without damaging healthy tissue, strains the patient only mildly, and can be produced and applied with a minimal effort.

This problem is solved according to the invention by a device designed or produced in accordance with the characteristics of claims 1 and 22. The dependent claims disclose further characteristics and advantageous improvements of the invention.

The invention provides improved drug-carrying balloon catheters or similar medical devices manufactured in a simple process that are highly versatile and facilitate the immediate release of active agents. Surprisingly, and contrary to the current school of thought, no continuing release of the active agent from an inert matrix (polymer, hydrogel, microcapsule, etc.) and no special chemical or physical state of the active ingredients is required or useful. Therefore, no sophisticated techniques for producing or controlling depot formulations are required. In many cases, vasoconstrictions obstruct the insertion of the balloon into the section of tissue to be treated. The diseased tissue sections or organ parts often comprise pathological stenoses. According to the invention, a balloon catheter that comprises at least one apparatus protruding from a balloon or sitting on the surface of the balloon for slitting stenoses at least in the vicinity of the diseased tissue sections or organ parts is used to place the drug-carrying balloon(s) inside the respective body cavities in the area of the tissue section or organ to be treated. The apparatus for slitting stenoses may consist of a wire-like device that is arranged in parallel to the longitudinal axis of the balloon. In particular, the apparatus is formed by two wire-like devices that form a grid-like design, the longitudinal axis of said grid-like design once again being arranged in parallel or axially parallel to the longitudinal axis of the balloon. The apparatus for slitting stenoses may also consist of at least one blade-like device or at least one projecting part protruding from the balloon or sitting on the surface of the balloon. Suitable materials for producing such a blade-like device are metals, metal alloys, plastics, or combinations thereof. In particular, so-called shape memory alloys may be used. Such an apparatus for slitting stenoses can be advantageously used, for example,

for slitting calcified vasoconstrictions or in-stent restenoses, which considerably increases the elasticity of the tissue sections treated in this way and improves access for the drugs.

Coating balloons on catheters with drugs according to this invention is particularly useful because there is a frequent need for treatment after blood vessels or other voids in the body were dilated with balloons to prevent stenosis or an occlusion of the lumen created under pressure using the balloon, to limit tumor growth or to enhance healing processes including the formation of collateral circulation. This can be achieved by drugs that become effective in the immediate vicinity of the balloon surface. The drugs firmly adhere to the balloon while passing through arteries with an intense blood flow on their way to their target until the balloon is inflated, and an effective dose is dispensed in the short time (sometimes just a few seconds) during which the balloon is in contact with the tissue, absorbed by the tissue in such a way that the blood flow that resumes immediately after the balloon is deflated does not rinse it off.

Wires used to guide catheters, as well as needles and catheters or catheter parts that are pressed against the diseased tissue at least for a short time may also be used for coating. Preferred catheter materials are polyamides, polyamide mixtures and copolymers, polyethylene terephthalate, polyethylene and copolymers, polyurethane, natural rubber and its derivatives. The lengths and diameters of the catheter or balloon areas designated for pharmacological treatment are not of any decisive importance for their application as the dosage is calculated in µg of active agent / mm^2 of surface area. For example, balloons with diameters ranging from 2 to 4 mm and lengths ranging from 1,0 to 4.0 cm are commonly used for coronary dilatation. Balloons > 20 mm in diameter and > 10 cm in length can be used for other vessels. The surfaces to be coated may be smooth (i. e. without a special structure for absorbing the active agents), roughed up or comprise any texture; while no special surface textures are required for the active agents to adhere, such textures also do not impede adhesion. Adhesion of the active agents to the balloon surfaces is exclusively caused by selecting suitable solvents and, optionally, adding substances that influence adhesion. It is even surprisingly strong on completely smooth balloon surfaces.

All surfaces can additionally be coated with substances that improve the gliding quality of the products, prevent blood from coagulating on the surface or improve any other properties these medical products have but the materials used for coating do not have to be released into the environment and this additional coating does not noticeably reduce the release of the active agents for treatment of the target tissue and thus the product's efficacy.

Balloon catheters are formed by dilating a segment from 1 cm to about 10 cm in length of very thin plastic hoses. The dilated, very thin-walled balloon membrane is then folded along the catheter axis and wrapped tightly around the catheter axis so that the dilated area, when folded, is only slightly greater in diameter than the rest of the catheter. The tight folding of the balloon membrane is required for passing the catheter through guiding sheaths, guiding catheters and severely stenosed sections of blood vessels.

The balloons of catheters can be coated when folded or when unfolded. The process always provides an intact and sufficient surface coating, and the active agents adhere to the surface of the balloon even when it is refolded after being coated when unfolded.

A balloon that was coated when unfolded is produced without any impact on the coating, for example by using balloon membranes with preformed folds and bends whose structure is not lost due to dilatation and which allow the balloon membrane to refold at least loosely when the pressure is discharged from the balloon without requiring an external causative force. It is only after this prefolding that the preformed folds are compressed by external pressure or by a vacuum. Folds are in no way required to hold the active agent. In addition, refolding can be achieved using minor mechanical force by very smooth materials, and the tools used may also be wetted by slippery biocompatible liquids in which the active ingredients do not dissolve or, at least, do not dissolve well.

According to another embodiment of the invention, the balloons of folded balloon catheters are coated by immersing them in low-viscosity solutions of active agent. Solvent and active agent penetrate into the extremely dense folds where they form a surprisingly uniform coat that contains a reproducible dose and is not damaged by any subsequent step. The solution or, after the solvent has dried, the coat that adheres to the outer side of the catheter may be left there or may be removed in another step so that only the active agent portion that sits inside the folds of the balloon is retained.

After coating, when the balloon is folded, a stent can be pulled over the balloon catheter and firmly pressed onto it. The only step still required is sterilization, e. g. using ethylene oxide.

The work cycle laid out like this is extremely simple, hardly susceptible to trouble, and can be carried out even with mechanically, chemically and physically sensitive coating materials. It was found that coating using this method does not result in any undesirable loosening or pasting together of the folds and that the active agent applied in this way adheres firmly enough to not be rinsed off by the bloodstream but releases most of the active agent when the balloon is inflated in the target tissue.

Suitable drugs are lipophilic, mostly water-insoluble and strongly acting drugs that bond to any tissue components. Drugs are called lipophilic when their butanol to aqueous buffer solution (pH 7) distribution ratio is ≥ 0.5, preferably ≥ 1 and particularly preferred ≥ 5, or when their octanol to aqueous buffer solution (pH 7) distribution ratio is ≥ 1, preferably ≥ 10, and particularly preferred > 50. Alternatively, or in addition to this, the drugs should reversibly and/or irreversibly bond to cell components at percentages $> 10\%$, preferably $> 50\%$, and particularly preferred $> 80\%$. Preferred are substances that inhibit cell proliferation or inflammatory processes, or antioxidants such as Paclitaxel and other taxanes, Rapamycin and related substances, tacrolismus and related substances, corticoids, sexual hormones (estrogen, estradiol, antiandrogens) and related substances, statins, epothilones, probucol, prostacyclins, inducers of angiogenesis, etc.

These substances are preferably present as a dry solid or as an oil on the surfaces of the various medical products. Preferred are the smallest particle sizes (mostly > 5 µm, preferably > 1 µm, particularly preferred > 0.1 µm), particularly preferred are amorphous non-crystalline structures of the finest particle size that dissolve fast upon contact with tissue due to their large surface area and despite their generally low solubility in water and do not function as microcapsules, i. e. dissolve spontaneously and fast. It is sufficient that an effective dose is present in the form of smallest or amorphous particles; larger particles hardly contribute to the active agent concentration in the tissue but do not cause any interference. The dosage depends on the desired effect and the efficacy of the drug used. It may be up to 5 µg/ mm² and this value does not even constitute an upper limit. It is easier to handle smaller dosages.

Good adhesion to the surfaces of catheters, needles or wires and an improved absorption by the tissues is achieved by embedding strongly lipophilic active agents with poor water solubility in a slightly water-soluble matrix substance. Suitable matrix substances are low-molecular (molecular weight < 5000 D, preferably < 2000 D) hydrophilic substances such as contrast agents and dyes used in vivo for various diagnostic procedures in medicine, sugar and related substances such as sugar alcohols, low-molecular polyethylene glycols, biocompatible organic and inorganic salts such as, for example, benzoates, salts and other derivatives of salicylic acid, etc. Examples of contrast agents are iodized X-ray contrast agents and paramagnetic chelates, examples of dyes are indocyanine green, fluorescein, and methylene blue. Adjuvants may improve storage life of the products, cause specific additional pharmacological effects or be instrumental for quality control.

In another embodiment of the invention, the pharmacologically active agents can be adsorbed to particles or applied to the surfaces of suitable medical products with a low-molecular matrix. Suitable particles once again are diagnostics known to be biocompatible such as ferrites and various contrast agents for sonography.

Adjuvants of any kind can be used at lower or higher doses than the active ingredients.

The medical products are coated using solutions, suspensions, or emulsions of the drugs and adjuvants mentioned above. Suitable media for solution, suspension or emulsion are, for example, ethanol, isopropanol, ethyl acetate, diethyl ether, acetone, dimethyl sulfoxide, dimethyl formamide, glycerin, water or mixtures thereof. Solvent selection is based on the solubility of the active agents and adjuvants, the wetting of the surfaces to be coated and the effect on the structure of the coating and particles remaining after evaporation, their adhesion to the surface and active agent transfer to the tissue in very short contact times.

Coating can be carried out by immersing, spreading, applying with volume gages or spraying at various temperatures and, optionally, vapor saturation of the solvents in the atmosphere. The procedure can be repeated several times using different solvents and adjuvants as may be required.

The balloons of folded balloon catheters can be given a surprisingly uniform, reproducible, dose-controllable coating without impairing catheter functionality by immersing them in solutions containing the active agent(s) or by other measures. When the balloons are repeatedly immersed in unsaturated active agent solutions, the active agent applied previously is not completely stripped off; instead, the active agent content of the balloons is increased in a reproducible manner.

Excess solution or excess substances from the coating solution that are loosely attached to the exterior can be removed with simple methods without impairing the efficacy of the coating.

The various types of medical apparatuses designed and manufactured according to the invention come into short-term contact with the tissue, i. e. for a few seconds, minutes, or hours. It is desirable in some cases to treat the tissue with drugs in the immediate vicinity of the medical product, e. g. to prevent excess growth as a response to an injury or to reduce tumor growth, to enhance vascularization of blood vessels or diminish inflammatory reactions. In all these cases, high local drug concentrations can be achieved for an astonishingly long time using the method

described above. A major advantage is the extraordinary versatility of uses of the products and methods described.

A preferred application is to reduce hyperproliferation of vessel walls induced by dilatation with balloon catheters. This can be achieved when optional stents are implanted by coating these stents with drugs, but only for the vessel section covered by the stent. The coated balloon catheters also treat any areas a short distance in front of and behind the stent that need treatment, they can treat the section where a stent has been implanted without requiring another stent implantation and vessels in which no stent is to be or can be implanted. An advantage as compared to the stents that release a drug over a longer period of time is improved implant healing and simultaneous good inhibition of hyperproliferation at a reduced risk of thrombosis.

Several embodiments of the invention will be described below with reference to examples regarding the coating of balloon catheters, adhesion of the coating in the bloodstream, restenosis inhibition and active agent content of the catheters.

Example 1:

Coating an expanded balloon catheter with Paclitaxel in an ethyl acetate solution

Balloon catheters made by BMT, Oberpfaffenhofen/Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are inflated to the maximum and immersed full length for 1 minute in ethyl acetate, 18.8 mg Paclitaxel per ml, +1 % pharmaceutical olive oil, then dried: Paclitaxel content 39 µg (after extraction with ethanol, HPLC).

Example 2:

Coating a folded balloon catheter with Paclitaxel in an ethyl acetate solution

Balloon catheters made by BMT, Oberpfaffenhofen/Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are immersed full length in folded

condition for 1 minute in ethyl acetate, 18.8 mg Paclitaxel per ml, +1 % pharmaceutical olive oil, then dried:
Paclitaxel content 69 µg.

Example 3:
Coating a folded balloon catheter with Paclitaxel in an ethyl acetate solution

a) Balloon catheters made by BMT, Oberpfaffenhofen/ Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are immersed full length in folded condition for 1 minute in ethyl acetate, 16.6 mg Paclitaxel per ml, and dried for 4 hours:
Paclitaxel content 54 µg.
b) Same procedure, but two times immersed for 5 seconds with 1 hour drying time after each immersion in solution A (= 3.33 ml ethyl acetate + 100.0 mg Paclitaxel):
Paclitaxel content 126 µg.
c) Same procedure, but four times immersed for 5 seconds with 1 hour drying time after each immersion in the same solution:
Paclitaxel content 158 µg.

Example 4:
Coating a balloon catheter with Paclitaxel in acetone

Dissolve 350 mg of Paclitaxel in 9.0 ml of acetone; balloon catheters made by BMT, Oberpfaffenhofen/Munich, Germany, product name Joker Lite, balloon dimensions 2.5 mm by 20 mm, are inflated to the maximum and immersed full length for 1 minute and removed. The solvent is dried for 12 hours at room temperature. Then the balloon is deflated and folded in the common way using a PTFE-coated tool. Optionally, you can crimp a stent of suitable dimensions onto the balloon:
29 µg of Paclitaxel on the balloon.

Example 5:

Coating a balloon catheter with Paclitaxel in acetone

a) Immersion of folded balloon catheters made by BMT, product name Allegro, balloon dimensions 2.5 by 20 mm in a mixture of 0.15 ml ethanol + 4.5 µl of Ultravist 300 (an X-ray contrast agent made by Schering AG, Berlin, Germany) + 1.35 ml of acetone + 0.8 mg of Sudan red + 30.0 mg of Paclitaxel:
The folded balloon sections of the catheters are immersed 5 times, the first time for one minute, then dried for 3 hours, then 4 times at 1 hour apart for 5 seconds each; subsequently, a stent was crimped on and the catheter was sterilized in the common way using ethylene oxide:
Paclitaxel content 172 microns, no decomposition products of the active agent were determined using HPLC

b) A saturated aqueous mannite solution is used instead of Ultravist 300

c) A saturated aqueous sodium salicylate solution (pH 7.5) is used instead of Ultravist 300

d) 5 mg of acetylsalicylic acid are added to the completed solution according to (5a).

e) 5 mg of glycerin are added to the completed solution according to (5a).

Example 6:

Adhesion of the active agent in the bloodstream

12 balloon catheters made by BMT, product name Allegro, balloon dimensions 2.5 by 20 mm, were used. A group of 6 of the folded balloon sections of the catheter was either 5 times immersed in [0.15 ml of ethanol + 4.5 µl of Ultravist 300 + 1.35 ml of acetone + 0.8 mg of Sudan red +30.0 mg Paclitaxel] or 5 times in [1.5 ml of ethyl acetate + 0.8 mg Sudan red + 31.0 mg Paclitaxel], the first time for 1 minute each with 3 hours of drying time, then 4 times for 5 seconds each at 1 hour intervals; then 3 of the folded balloons of each group were gently moved for 5 minutes at 37°C in 50 ml of human blood and removed to determine the Paclitaxel content:
Reduction of the mean values (n=3 per coating method) by moving the catheters in

blood in comparison to 3 control catheters that were not moved in blood.

acetone: 12 %

ethyl acetate: 10 %

Example 7:

Examination of restenosis inhibition after angioplasty and stent implantation in coronary arteries of pigs

Folded balloon catheters of the Joker Lite type made by BMT, 3.5 by 20 mm or 3.0 by 20 mm were immersed for 1 minute either in

solution A) 3.33 ml of ethyl acetate (EA)+ 100.0 mg of Paclitaxel,

or in

solution B) 0.45 ml of ethanol + 100 µl of Ultravist-370 + 4.5 ml acetone (ac) + 150.0 mg Paclitaxel

and dried over night at room temperature. One more (low dose = L) or 4 more (high dose = H) immersion process(es), respectively, were carried out for just five seconds at 1 hour intervals on the next day.

Active agent content after 2 immersions in solution (B) averaged 250 µg, after 5 immersions in solution (B) 500 µg, in solution (A) 400 µg.

The catheters coated with Paclitaxel or uncoated were used to implant stents into the left anterior or lateral coronary artery of a total of 22 pigs, and the vessels were slightly dilated to stimulate restenosis by tissue hyperplasia. The animals were reangiographed after 5 weeks, and the vessel contraction shown in the angiograms was measured using an automatic computer program.

Group	Stenosis (%)
Uncoated	50.49
AcL	20.22
EAH	36.01
AcH	0.86
P	.004

Quantitative coronary angiography 5 weeks after stent implantation with uncoated and

coated catheters; stenosis = reduction of lumen diameter in percent in the area of the stent as compared to the lumen diameter immediately after stent implantation; mean value and statistical significance of the effect of treatment.

Example 8:

Active agent content of the catheters after vessel dilatation and stent implantation

After stent implantation and removal from the animals, a piece of the balloons from Example 8 ca. 3 cm in length was cut off the balloon catheters and placed in 1.5 ml of ethanol. Paclitaxel content was determined using HPLC. All available coated balloons and a selection of uncoated balloons were examined.

Coronary,

3.0 by 20 mm, coating:	Ac high	38 ± 4 µg (n=4)
	Ac low	22 ± 5 µg (n=2)
	EEE high	41 (n=1)
3.5 by 20 mm, coating:	Ac hig	37± 10 µg (n=8)
	Ac low	26 ± 6 µg (n=8)
	EEE high	53 ± 9 µg (n=9)
Uncoated (independent of size and vessel area)		0.9 ± 1.0 µg (n=7)

It follows from Example 6 that a maximum of 10% of the dose is lost before the balloon is inflated and about 10% of the dose remain on the balloon.

Example 9:

Probucol is added to acetone at a concentration of 100 mg per ml; the solution is used to coat balloon catheters as described in the above examples.

Example 10:

Rapamycin is dissolved at a concentration of 10 mg/ml in diethyl ether. The balloon sections of the catheters are coated as described in the above examples; after removal

from the coating solution, the balloons should be brought into a horizontal position and continuously be turned around their longitudinal axis.

Example 11:
Epothilone B is added to ethyl acetate at a concentration of 2 mg/ml; the solution is used to coat balloon catheters as described in the above examples.

A schematic view of an embodiment of the invention showing one design of the medical device 10 is shown in the figure below. The device 10 consists of a balloon catheter 12 with a catheter 22 and a balloon 14 and an apparatus 24 protruding from the balloon 14 for slitting stenoses at least in the area of the diseased tissue sections or organ parts. According to the embodiment shown, the apparatus 24 for slitting stenoses consists of six wire-like devices 18 that form a grid-like design. The longitudinal axis of the grid-like design is axially parallel to the longitudinal axis of the balloon 14. The grid-like design is held at its end by first and second joining elements 18, 20. The joining elements 18, 20 do not only hold the wire-like devices 18 but are also used for fastening the grid-like design to the catheter 22. Other embodiments with one or several wire-like devices 16 are conceivable.

The apparatus for slitting stenoses may also consist of at least one blade-like device or at least one projecting part protruding from the balloon or sitting on the surface of the balloon (not shown).

Suitable materials for producing the blade-like device 16 are biocompatible metals such as stainless steel, metal alloys, plastics, or combinations thereof. In particular, shape memory alloys such as Nitinol may be used.